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Abstract

Context. The safety of mefloquine, a common antimalarial drug sold under the trade name Lariam, has not been well described in military populations.

Objective. To use readily available electronic data to determine mefloquine prescriptions and disease outcomes, as measured by hospitalization, to study mefloquine safety among US service members from 2002 through 2004.

Design. Using an electronic pharmaceutical database, 8858 mefloquine-prescribed and deployed personnel were identified and compared with 2 reference groups. The reference groups comprised US service members who were not prescribed mefloquine and resided in Europe or Japan (n = 156 203) or had been otherwise deployed (n = 232 381) during the study period. Hospitalizations and diagnoses were assessed from standard military databases, and differences in these outcomes were evaluated using Cox proportional hazards modeling.

Main Outcome Measure. Broad illness and injury categories, as well as specific mental health groupings identified through Department of Defense hospitalization data.

Results. In comparison with active-duty US service members residing in Europe or Japan, US service members were at a statistically significant decreased hazard for any-cause hospitalization, as well as to diseases of the respiratory and digestive systems, musculoskeletal system and connective tissue diseases, injuries and poisonings, ill-defined conditions, and mood disorders.

Conclusions. These results suggest there is no association between mefloquine prescriptions and severe health effects, as measured by hospitalizations, across a wide range of outcomes.

It is estimated that malaria infects more than 500 million people and causes between one and three million deaths annually.[1] Recently, 80 of 290 US Navy, Marine Corps, and Army personnel developed malaria during or shortly after deployment to Liberia.[2] One hundred fifty-seven deployed US Marines were interviewed and 95% reported no missed mefloquine doses. However, serum mefloquine levels indicated only 7 of 133 service members had been compliant with the dosing schedule, leading to speculation that poor compliance was a result of circulating rumors regarding the neuropsychiatric adverse effects associated with mefloquine use.[3,4] During Operation Enduring Freedom, 38 of 725 US Army Rangers contracted malaria.[5] A postdeployment survey identified that those who experienced adverse events while taking antimalarials were most likely to be noncompliant with mefloquine.

Mefloquine, a quinoline methanol drug sold under the trade name Lariam, was approved by the Food and Drug Administration on May 2, 1989, for malaria chemoprophylaxis.[6] In 1990, the Centers for Disease Control and Prevention (CDC), recommended mefloquine for the prevention of malaria in areas with chloroquine-resistant *Plasmodium falciparum*.[7] In its recommendation, CDC stated that mefloquine had, on rare occasion, been associated with hallucinations or convulsions at prophylactic doses, and cautioned that it was not recommended for travelers with a history of psychological disorder. Since the publication of *Health Information for International Travel, 2001-2002*, CDC has recommended Malarone, doxycycline, or mefloquine for travelers going to areas with chloroquine-resistant *P. falciparum*.[8,9]

Although mefloquine remains very effective at preventing malaria, case reports, as well as observational and experimental epidemiological studies, have associated mefloquine use with acute psychoses, seizures, vivid dreams, anxiety neurosis, depression, hallucinations, poor sleep patterns, paranoia, suicidal ideation, visual illusions, multifocal myoclonus, and trigeminal sensory neuropathy.[10-26]

Observational studies and randomized clinical trials have found that those who took mefloquine were at increased risk for a wide variety of neuropsychiatric events, including depression, dizziness, panic attacks, strange thoughts, altered spatial perception, fatigue, headache, and vivid dreams.[27-36] It has also been observed that women report the greatest number of adverse events, as well as first-time users.[37] In contrast, several observational epidemiological studies and a few clinical trials have reported that mefloquine is safe and well tolerated, especially among military populations.[38-42]

Safe and effective antimalarials are of great importance to the health of US service members. Studies of civilian populations may not apply to military forces since this group represents a unique population with differences in demographic composition, health, environmental exposures, and purpose of travel in comparison with most civilian cohorts studied to date. The objective of this study was to describe serious health outcomes after mefloquine use among US service members.

METHODS

Study Population

The study cohort included all active-duty US service members during the period January 1, 2002, and December 31, 2002, as reported by the Defense Manpower Data Center (DMDC), Monterey, California. The mefloquine-prescribed group was defined as service members who had been prescribed a minimum of 7 mefloquine tablets beginning in 2002 and who were identified as having been deployed at some point during the same time period. Mefloquine prescriptions were identified using the Military Health Systems Management Analysis and Reporting Tool.[43] This file dates back to October 2001, and includes personal identifiers, drug name, number of tablets dispensed, and date of transaction for the drugs prescribed. Deployment was defined through DMDC pay files as evidence of having received either combat zone tax

exclusion or imminent danger pay. In instances where there was more than one qualifying prescription-deployment combination, the first occasion was chosen for this study.

We used 2 reference groups. The first reference group comprised service members who had duty zip codes for either Europe or Japan at some time during 2002, and had no evidence of having been deployed from October 1, 2001, through the individual's period of observation. This group was chosen to represent those healthy enough to be stationed overseas and healthy enough to have taken mefloquine during the study period. The second reference group consisted of US service members who were identified as having been deployed for a minimum of 1 month during 2002. Both reference groups were restricted to individuals who had no evidence of having received a prescription for mefloquine or chloroquine, or a doxycycline prescription for more than 14 tablets. Excluding all antimalarials was done to ensure the reference groups did not include mefloquine-prescribed people not represented in the prescription database.

Hospitalization Diagnoses

The study cohort was electronically linked to the Standardized Inpatient Data Record (SIDR) and the Health Care Service Record (HCSR) to identify hospitalizations. The SIDR record may contain up to 8 *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*)-coded[44] diagnoses per admission, while the HCSR inpatient record contains an admission, a primary, and up to 8 secondary *ICD-9-CM*-coded diagnoses. For this study, each unique diagnosis was included in the analysis. We analyzed any-cause hospitalization [excluding complications of pregnancy, childbirth and the puerperium (630-676), congenital anomalies (740-759), and certain conditions originating in the perinatal period (760-779)]. Other a priori outcomes included hospitalizations among 14 broad *ICD-9-CM*-coded categories, including infectious and parasitic diseases (001-139); neoplasms (140-239); endocrine, nutritional, and metabolic diseases, and immunity disorders (240-279); diseases of the

blood and blood-forming organs (280-289); mental disorders (290-319); diseases of the skin and subcutaneous tissue (680-709); symptoms, signs, and ill-defined conditions (780-799); injury and poisoning (800-999); and diseases of the following systems: nervous and sense organs (320-389), circulatory (390-459), respiratory (460-519), digestive (520-579), genitourinary (580-629), and musculoskeletal and connective tissue (710-739). Mental disorder diagnoses were stratified into 5 categories, including somatoform, mood, anxiety, substance use, and other disorders.[45] In addition, hospitalizations due to migraine (346), nystagmus associated with disorders of the vestibular system (379.54), vertiginous syndromes, and other disorders of vestibular system (386), and dizziness and giddiness (780.4) were analyzed.[46]

Statistical Analysis

Statistical analyses included both descriptive and multivariable methods. After descriptive investigation of population characteristics, analyses were performed to assess the significance of associations between mefloquine prescription and sex, age, race/ethnicity, service, marital status, rank, occupation, and history of hospitalization during 2001 in comparison with both reference groups. Age was grouped into 3 categories ($\leq$24, 25-34, and $\geq$35 years). Service branches included Army, Navy, Marines, and Air Force. Race/ethnicity included black non-Hispanic, Hispanic, other, and white non-Hispanic. Marital status was categorized as married and nonmarried. Pay grade was dichotomized to enlisted and officers, and occupations included combat and noncombat.

Cox proportional hazards time-to-event modeling was employed to compare the hospitalization experience among mefloquine-prescribed US service members with the hospitalization experience among those stationed in Europe/Japan and the deployed reference groups, while accounting for attrition from active duty service during the follow-up period. Follow-up time began upon return from deployment for mefloquine-prescribed members and for

the deployed reference group, and upon assignment to Europe or Japan, or January 1, 2002, whichever occurred last for the Europe/Japan reference group. Follow-up continued for 12 months or until date of separation from active-duty service, date of next deployment, date of next antimalarial prescription, or end of the study period, March 31, 2004, whichever occurred first. Individuals who could not be followed a minimum of 2 months were excluded from the study. Statistical analyses including adjusted hazard ratios (HRs) and associated 95% confidence intervals (CIs) were performed by using SAS® software (Version 9.1, SAS Institute Inc., Cary, NC).[47]

RESULTS

We identified a cohort of 8858 mefloquine-prescribed service members, 156 203 individuals with duty zip codes of Europe or Japan, and 232 381 deployed military members without mefloquine prescriptions (Table 1). Although the differences in proportional distribution within each variable were statistically significant ($P<0.001$) when comparing the mefloquine prescribed group with the 2 reference groups, the most striking differences occurred among the services. Navy and Marine Corps personnel were significantly underrepresented in the mefloquine-prescribed group, while the mefloquine-prescribed group had a larger percentage of members who were in infantry, gun crew, or seaman specialties. Among the variables considered, initial analyses indicated that age, sex, military rank, race/ethnicity, service branch, marital status, occupation, and previous hospitalization were significantly associated with hospitalizations (2-sided $P\leq0.05$), and these covariates were entered into the Cox proportional hazards models.

In multivariable Cox proportional hazards modeling only 5 of 14 *ICD-9-CM* broad categories, in addition to any-cause hospitalization, were statistically significant when compared with the Europe/Japan reference group (Table 2). The mefloquine-prescribed group was at

significantly lower risk for hospitalizations due to any cause (HR, 0.47; 95% CI, 0.39-0.56), diseases of the respiratory system (HR, 0.44; 95% CI, 0.23-0.86), digestive system (HR, 0.52; 95% CI, 0.34-0.79), musculoskeletal system and connective tissue (HR, 0.68; 95% CI, 0.47-0.98), ill-defined conditions (HR, 0.24; 95% CI, 0.16-0.37), and injuries and poisonings (HR, 0.63; 95% CI, 0.47-0.84) after adjusting for age, sex, military rank, race/ethnicity, service branch, marital status, occupation, and previous hospitalizations during 2001. There were no statistically significant differences when compared with the deployed reference group.

Multivariable Cox proportional hazards analyses were conducted for specific categories of psychiatric and neurological hospitalizations (Table 3). Mefloquine-prescribed individuals were at significantly decreased risk of hospitalizations for mood disorders when compared with the Europe/Japan reference group (HR, 0.37; 95% CI, 0.15-0.90), after adjusting for age, sex, military rank, race/ethnicity, service branch, marital status, occupation, and previous hospitalizations. No other psychiatric or neurological categories were statistically significant when the mefloquine-prescribed group was compared with either reference group.

COMMENT

This is the first study to assess morbidity associated with mefloquine solely using hospitalizations as an objective measure of health among members of the US military. Using 2 reference populations, we found little evidence that mefloquine-prescribed active-duty service members were at increased risk for hospitalizations over a broad range of outcomes, including mental disorders, and diseases of the nervous system.

In comparison with military members stationed in Europe or Japan, mefloquine-prescribed individuals were at a significantly decreased risk for hospitalizations due to any cause, diseases of the respiratory and digestive systems, and hospitalizations due to musculoskeletal and connective tissue, ill-defined conditions, injuries and poisonings, and mood disorders. It is

possible, but quite unlikely, that mefloquine use provides some protective effect for these outcomes. More likely, these decreased hazard ratios are the result of a selection, or reporting, bias. We chose service members living in Europe or Japan because they undergo a medical clearance process prior to being assigned overseas, where health care services may be limited. However, we restricted this group to those with no evidence of having been deployed, so members of this group may not have been as healthy as the mefloquine-prescribed group, all of whom had deployed. Another possible explanation for these findings is service members who reside in Europe or Japan might be hospitalized for less-severe conditions than are those in the United States, or perhaps overseas hospitalizations are more likely to be reported.

Finding an elevated, but not statistically significant, hazard for vertiginous syndromes when compared with both reference groups is interesting. Recently, there has been much interest in the relationship between mefloquine and vertiginous syndromes in the media and among federal legislators.[46] Further studies are required to better assess whether an association between mefloquine and vertiginous syndromes exists.

The unique nature of this study makes comparisons with previously published results difficult. Of those published, a study by Meier and colleagues was most similar in methodology utilizing electronically recorded prescriptions and diagnoses to define exposure and outcome, respectively.[30] However, remaining differences in study design and the coding of neuropsychiatric outcomes between the 2 studies makes comparisons hard. Although different in methodologies, it might be reassuring that the absence of significant risk for severe neuropsychiatric illnesses among service members taking mefloquine was observed in this study, 3 randomized clinical trials, and 1 open-label prospective study using military populations.[35,36,39,42]

The results of this study should be considered within its limitations. Using a prescription database as a surrogate for mefloquine exposure created unique challenges, including potentially low sensitivity for identifying exposure. We attempted to minimize exposure misclassification by requiring a minimum pill count of at least 7 tablets per mefloquine prescription to qualify as an exposure, yet we acknowledge this serves only as a proxy for having taken mefloquine. Among the deployed reference group, there may have been poor specificity in mefloquine exposure assessment since an unknown percentage of individuals in this population may have actually taken mefloquine while deployed. We attempted to improve specificity of mefloquine exposure by using a reference group containing only nondeployed service members who resided in Europe or Japan. Although we chose to assess hospitalizations as the outcome measure for this study, this choice restricted analyses to those medical conditions that were of ample severity to require hospitalization, and it does not represent the entire spectrum of morbidity that may be associated with mefloquine. Finally, the study design called for a large number of analyses, which increases the likelihood of finding a statistically significant, but spurious, association.

This study has a number of strengths. It was specifically designed to assess the association between mefloquine prescriptions and hospitalizations among US military personnel, an otherwise healthy population of younger adults. We identified an adequate number of mefloquine-prescribed individuals and 2 large reference groups to allow adequate power to explore associations, with the exception of very rare outcomes. The use of 2 reference groups allowed for comparisons with a population that had high specificity for mefloquine exposure, the Europe/Japan reference group. While the deployed reference group had some potential for misclassification of mefloquine exposure, this group was more homogeneous in comparison with the mefloquine-prescribed group. Although the use of hospitalization data limited the number of

outcomes available for analysis, the use of these objective data eliminated the possibility of recall bias.

This study was the first to describe the relations between mefloquine-prescribed US service members and a wide range of health outcomes using objective data. We found that mefloquine-prescribed service members were not at a statistically significant increased risk for hospitalization over a wide range of broad and specific disease categories. Future studies should explore additional data sources that complement those used in this study to define mefloquine exposure and neuropsychiatric outcomes.

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Table 1. Demographic Characteristics of Mefloquine-Prescribed US Military Personnel, Residing in Europe or Japan, or Deployed, 2002-2003

Characteristic*	Mefloquine[†] (n = 8858)	Europe/Japan[‡] (n = 156 203)	Deployed[§] (n = 232 381)
Sex			
Male	8245 (93.1)	128 973 (82.6)	208 435 (89.7)
Female	613 (6.9)	27 230 (17.4)	23 946 (10.3)
Age, y			
17-24	4516 (51.0)	73 081 (46.8)	109 645 (47.2)
25-34	2943 (33.2)	51 634 (33.0)	74 459 (32.0)
≥35	1399 (15.8)	31 488 (20.2)	48 277 (20.8)
Marital status			
Single	6360 (71.8)	106 220 (68.0)	156 977 (67.6)
Married	2498 (28.2)	49 983 (32.0)	75 404 (32.4)
Race/ethnicity			
White non-Hispanic	6084 (68.7)	93 660 (60.0)	153 254 (65.9)
Black non-Hispanic	1477 (16.7)	35 891 (23.0)	43 313 (18.6)
Hispanic	853 (9.6)	15 224 (9.8)	21 489 (9.3)
Other	444 (5.0)	11 428 (7.2)	14 325 (6.2)
Service			
Army	7028 (79.3)	62 334 (39.9)	59 075 (25.4)
Air Force	1663 (18.8)	38 566 (24.7)	66 688 (28.7)
Marine Corps	95 (1.1)	18 493 (11.8)	23 112 (9.9)
Navy	72 (0.8)	36 810 (23.6)	83 506 (35.9)
Rank			
Enlisted	8032 (90.7)	144 406 (92.4)	206 326 (88.8)
Officer	826 (9.3)	11 797 (7.6)	26 055 (11.2)
Occupational category			
Infantry, gun crews, seamen	3296 (37.1)	24 773 (15.8)	60 769 (26.2)
Mechanical equipment repair	811 (9.2)	27 569 (17.6)	51 351 (22.1)
Functional support and admin	1141 (12.9)	29 938 (19.2)	30 254 (13.0)
Electrical repair	616 (7.0)	15 697 (10.1)	23 768 (10.2)
Service and supply	925 (10.4)	17 073 (10.9)	18 707 (8.1)
Communication/intelligence	858 (9.7)	13 961 (8.9)	22 369 (9.6)
Health care	416 (4.7)	12 110 (7.8)	7756 (3.3)
Construction	233 (2.6)	6552 (4.2)	8348 (3.6)
Other technical and specialty	350 (4.0)	4351 (2.8)	6512 (2.8)
Other and missing	212 (2.4)	4179 (2.7)	2547 (1.1)
Previous hospitalization in 2001	223 (2.5)	3495 (2.2)	3983 (1.7)

*All chi-square tests of significance were statistically significant at $P<0.001$.

[†]Prescribed 7 or more mefloquine tablets.

[‡]Residing in either Europe or Japan during 2002, with no electronic prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

[§]Deployed for 1 or more months during 2002, with no electronic prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

Table 2. Results of Cox Proportional Hazards Analysis for Hospitalizations Among US Service Members Prescribed Mefloquine, 2002-2003

	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs Deployed†
Category (*ICD-9-CM* codes)	Mefloquine (n)	Euro/Japan* (n)	Deployed† (n)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Any cause¶	135	7308	5868	0.47 (039-0.56)	0.94 (0.79-1.12)
Infectious/parasitic (001-139)	11	386	438	1.06 (0.57-1.94)	1.08 (0.59-1.99)
Neoplasms (140-239)	5	240	251	0.90 (0.37-2.21)	1.13 (0.46-2.77)
Endocrine, nutritional, metabolic (240-279)	13	416	493	1.04 (0.59-1.82)	1.34 (0.77-2.35)
Blood and blood-forming organs#	4	316	360	0.51 (0.19-1.36)	0.65 (0.24-1.74)
Mental disorders (290-319)	37	1280	1314	0.76 (0.55-1.07)	1.23 (0.87-1.72)
Nervous system (320-389)	6	312	292	0.58 (0.26-1.32)	0.76 (0.34-1.73)
Circulatory system (390-459)	9	492	577	0.61 (0.31-1.18)	0.69 (0.35-1.34)
Respiratory system (460-519)	9	578	486	0.44 (0.23-0.86)	0.81 (0.42-1.58)
Digestive system (520-579)	23	1280	1122	0.52 (0.34-0.79)	0.90 (0.60-1.37)
Genitourinary system (580-629)	13	724	512	0.71 (0.40-1.26)	1.19 (0.67-2.13)
Skin and subcutaneous tissues (680-709)	9	272	294	0.88 (0.43-1.80)	1.31 (0.64-2.69)
Musculoskeletal and connective tissue (710-739)	30	1149	984	0.68 (0.47-0.98)	1.28 (0.88-1.85)
Ill-defined conditions (780-799)	22	2255	1221	0.24 (0.16-0.37)	0.71 (0.46-1.09)
Injury and poisoning (800-999)	47	1798	1802	0.63 (0.47-0.84)	1.06 (0.79-1.43)

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; Euro, Europe; HR, hazard ratio; CI, confidence interval.

*US service members who resided in either Europe or Japan during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

†US service members who deployed for 1 or more months during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

‡Hazard ratio for mefloquine-prescribed group, using the Europe/Japan reference group.

§Hazard ratio for mefloquine-prescribed group, using the Deployed reference group.

¶Excludes complications of pregnancy, childbirth, and the puerperium (*ICD-9-CM* codes 630-676 and 740-779).

#*ICD-9-CM* codes 280-289.

Table 3. Results of Cox Proportional Hazards Analysis for Hospitalizations Among US Service Members Prescribed Mefloquine, Specific Psychological and Neurological Diagnoses, 2002-2003

	Cases			Mefloquine vs Europe/Japan*	Mefloquine vs Deployed†
Category (*ICD-9-CM* codes)	Mefloquine (n)	Euro/Japan* (n)	Deployed† (n)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Somatoform disorders‡	0	25	10	--	--
Mood disorders§	6	388	412	0.37 (0.15-0.90)	0.50 (0.21-1.22)
Anxiety disorders¶	6	186	185	0.92 (0.40-2.10)	1.27 (0.55-2.91)
Posttraumatic stress disorder (309.81)	1	38	29	0.79 (0.11-5.91)	1.66 (0.21-12.85)
Mixed syndromes#	4	130	151	0.91 (0.33-2.51)	0.99 (0.36-2.73)
Substance use disorders**	19	634	741	0.72 (0.45-1.15)	1.20 (0.75-1.90)
Other disorders††	20	743	551	0.71 (0.45-1.13)	1.54 (0.96-2.46)
Personality disorders (301)	7	364	225	0.46 (0.21-1.05)	1.39 (0.60-3.20)
Adjustment reaction‡‡	13	453	305	0.78 (0.45-1.38)	1.68 (0.95-2.97)
Nystagmus (379.5)	0	0	2	--	--
Vertiginous syndromes (386)	1	4	6	3.17 (0.32-31.18)	5.53 (0.59-52.06)
Dizziness and giddiness (780.4)	0	42	21	--	--
Migraine (346)	3	93	52	0.92 (0.40-2.10)	2.09 (0.63-6.90)

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; HR, hazard ratio; CI, confidence interval.

*Residing in either Europe or Japan during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

†Deployed for 1 or more months during 2002, with no prescription for mefloquine, chloroquine, or more than 14 tablets of doxycycline.

‡*ICD-9-CM* codes 300.11, 300.7, 300.81, 306, 307.80-307.81, 309.82, 316.

§*ICD-9-CM* codes 296.00, 296.2-296.3, 296.40-296.99, 298.0, 300.4-300.5, 311.

¶*ICD-9-CM* codes 300.0, 300.2-300.3, 300.89-300.9, 309.81.

#*ICD-9-CM* codes 300.00, 300.09, 300.2-300.3, 300.89-300.9.

***ICD-9-CM* codes 303, 304, 305.00-305.70.

††*ICD-9-CM* codes 290-294, 295.30, 295.60, 295.62, 295.70, 295.90, 297.9, 298.8-298.9, 300.12, 300.14, 300.16, 300.19, 301, 302.7, 307.0-307.2, 307.4-307.6, 307.9-310, 312-315, 317, 319.

‡‡*ICD-9-CM* codes 308-309.4, 309.83-309.9.

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14. ABSTRACT (maximum 200 words)

Context. The safety of mefloquine, sold under the trade name Lariam, has not been well described in military populations.
Objective. To use electronic data to determine mefloquine prescriptions and disease outcomes, as measured by hospitalization, to study mefloquine safety among US service members from 2002 through 2004.
Design. Using an electronic pharmaceutical database, 8858 mefloquine-prescribed and deployed personnel were identified and compared with 2 reference groups. The reference groups comprised US service members who were not prescribed mefloquine and resided in Europe or Japan (n = 156 203) or had been otherwise deployed (n = 232 381). Hospitalizations were assessed from standard military databases, and differences in outcomes were evaluated using Cox proportional hazards modeling.
Main Outcome Measure. Illness and injury hospitalization data.
Results. In comparison with US service members residing in Europe or Japan, US service members were at a statistically significant decreased hazard for any-cause hospitalization, as well as to diseases of the respiratory and digestive systems, musculoskeletal system and connective tissue diseases, injuries and poisonings, ill-defined conditions, and mood disorders.
Conclusions. These results suggest there is no association between mefloquine prescriptions and severe health effects, as measured by hospitalizations, across a wide range of outcomes.

15. SUBJECT TERMS
mefloquine, military health, hospitalizations, antimalarial

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